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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,126	03/14/2001	Torben Halkier	3631-0108P	6308
2292	7590	04/29/2004	EXAMINER	
BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 22040-0747			NICHOLS, CHRISTOPHER J	
		ART UNIT		PAPER NUMBER
		1647		
DATE MAILED: 04/29/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/787,126	HALKIER ET AL.
	Examiner	Art Unit
	Christopher J Nichols, Ph.D.	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 12 January 2004.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1,3,5,8-12,17-24,28,57 and 58 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1,3,5,8-12,17-24,28,57 and 58 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) 1,3,5,8-12,17-24,28,57 and 58 are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date _____.
 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____.

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12 January 2004 has been entered.

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendment filed 14 March 2001 has been received and entered in full.
3. The Preliminary Amendment filed 9 October 2001 has been received and entered in full.
4. The Amendment filed 7 April 2003 has been received and entered in full.
5. The Amendment filed 12 August 2003 has been received and entered in full.
6. The Declaration under 37 C.F.R. §1.132 filed 12 August 2003 has been received and taken into consideration.

Withdrawn Objections And/Or Rejections

7. All previous Objections and Rejections are hereby *withdrawn* in view of amendments and in the interest of expedited examination.

Priority

8. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Denmark on 15 September 1998. It is noted, however, that applicant has not filed a certified copy of the DENMARK PA 1998 01164 application as required by 35 U.S.C. 119(b).

Sequence Rules

9. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein. This application discloses nucleic acid sequences on pp. 43 lines 8-9. Correction is required.

Claim Objections

10. Claims 11, 12, and 22 are objected to because of the following informalities: claims 11 and 12 use the phrase "is selected from" and claim 22 uses the phrase "selected from the parenteral route selected from" none include a proper Markush group. This phrasing is awkward and may lead to confusion. The Examiner respectfully submits that Applicant should clarify whether or not a Markush group is present in the claim or whether the claim refers to a single limitation of a multiple number in the alternative. Appropriate correction is required.

11. Claim 28 is objected to because of the following informalities: the claim should include a comma following "at least 1". Appropriate correction is required.

Obvious-Type Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1, 3, 5, 8-12, 17-24, 57, and 58 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,645,500. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the claims of the instant application and US 6,645,500 encompass a method of using a modified OPGL polypeptide to down-regulate endogenous OPGL activity in an animal comprising administering to said animal a modified OPGL polypeptide comprising the insertion of T cell epitopes.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 3, 5, 8-12, 17-24, 57, and 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method for in vivo down-regulation of osteoprotegerin ligand (OPGL) activity in an animal, the method comprising effecting presentation to the animal's immune system of an immunologically effective amount of at least one modified OPGL polypeptide thereof which has a result that immunization of the animal with the modified OPGL polypeptide thereof induces production of antibodies against the animal's own OPGL polypeptide which down-regulates the animal's own OPGL activity,*

wherein said modified OPGL polypeptide thereof comprises the sequences of SEQ ID NO: 2 wherein at least one B-cell epitope is introduced in said sequence at residues 159-317, does not reasonably provide enablement for other permutations of the claimed formula, substitutions, mutations, insertions, deletions, and alterations of the amino acid sequence SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.

14. The Specification teaches that the growth, development, and maintenance of bone is a highly regulated process balanced between the opposing activity of two cells, osteoblasts (derived from mesenchymal stem cells) which make bone and osteoclasts (derived from hematopoietic precursors of the monocytes-macrophage lineage) which breakdown bone (resorption). The Specification teaches that disruption of the harmonious counteraction of osteoblasts and osteoclasts can lead to skeletal abnormalities characterized by either increased bone mass (osteopetrosis) or decreased bone mass (osteoporosis) (pp. 2-3). Osteoprotegerin is a novel secreted member of the tumor necrosis factor receptor family which blocks

osteoclastogenesis *in vitro* in a dose dependent manner (pp. 3). Osteoprotegerin ligand (OPGL) binds to osteoprotegerin and osteoclasts. OPGL is a potent activator of mature osteoclasts which leads to an increase in bone resorption (pp. 6 lines 8-20). The amino acid sequence of SEQ ID NO: 2 is human OPGL has 317 amino acids comprising 4 domains: a cytoplasmic domain from residues 1 to 48, a putative transmembrane domain from residues 49 to 69, an extracellular domain with a stalk region from residues 70 to 157 and an active ligand moiety from residues 158 to 317. OPGL has three known three active fragments consisting of residues 128-316, 137-316, and 158-316 all of which bind and activate osteoclasts *in vitro* (pp. 5 lines 8-26). A fourth fragment of OPGL consisting of residues 75-316 has no biological activity (pp. 5 lines 24-26). OPGL is also known as TRANCE, RANKL, and ODF (osteoclasts differentiation factor) (pp. 5 lines 1-7; see also Figure 2 of Takahashi *et al.* (24 March 1999) "A New Member of Tumor Necrosis Factor Ligand Family, ODF/OPGL/TRANCE/RANKL, Regulates Osteoclast Differentiation and Function." Biochemical and Biophysical Research Communications **256**(3): 449-455).

15. Applicant puts forth the proposition that OPGL and osteoprotegerin act as positive and negative regulators of osteoclasts development and activity, wherein OPGL promotes bone resorption via activation of mature osteoclasts and osteoprotegerin inhibits bone resorption via inhibition of osteoclasts development. This is support by four lines of evidence: (1) injection of mice with recombinant C-terminal domain of OPGL results in severe hypercalcemia (according to Stedman's Medical Dictionary: "An abnormally high concentration of calcium compounds in the circulating blood; commonly used to indicate an elevated concentration of calcium ions in the blood), (2) osteoprotegerin-deficient mice (knock-out mice) develop early onset osteoporosis, (3)

mice transgenic for osteoprotegerin develop osteopetrosis, and (4) mice injected with recombinant osteoprotegerin develop osteopetrosis (pp. 7 lines 1-25).

16. The Examiner notes that while the Applicant has presented a number of active OPGL polypeptides (full-length and the fragments consisting of residues 128-316, 137-316, and 158-316) and that it is entirely possible to use said OPGL polypeptides in a method of immunization to reduce serum OPGL, the claims are drawn very broadly to methods of a vast number of B-cell epitope and OPGL moiety combinations.

17. The specification fails to provide any guidance for the successful synthesis, isolation, and characterization of OPGL polypeptides beyond the full-length OPGL and OPGL fragments consisting of residues 128-316, 137-316, and 158-316. And since resolution of the various complications in regards to targeting the effect of mutations in a protein, the immunological effect of mutation, the effects of the modified polypeptide in an animal, and the immune response to as of yet described OPGL and B-cell epitope moieties is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations of all the applicable OPGL-B-cell moiety combinations. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

18. Additionally, a person skilled in the art would recognize that predicting the efficacy of using these ill defined, untested, and hypothesized OPGL-B-cell moieties *in vivo* based solely on

its indirect evidence is highly problematic (see MPEP §2164.02). Furthermore the Applicant states that: "The *in vivo* evidence is partially circumstantial or indirect but is in our opinion..." (pp. 7 lines 3-4), although the specification prophetically considers and discloses general methodologies of using the claimed methods of the undisclosed OPGL-B-cell moieties, such a disclosure would not be considered enabling since the state of protein biochemistry and immunology is highly unpredictable. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

19. The following references are cited herein to illustrate the state of the art of osteoporosis and immunology.

20. On the nature of the invention, US 6,645,500 B1 (11 November 2003) Halkier & Haaning teaches a similar invention wherein a T cell epitope is inserted into OPGL but US 6,645,500, unlike the instant claims, specifies the position of insertion. This is crucial to the success of the method because the skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional

changes in biological activity and immunological recognition, see in particular Skolnick & Fetrow (2000) "From genes to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39. For example, Jobling & Holmes (1991) "Analysis of structure and function of the B Subunit of cholera toxin by the use of site-directed mutagenesis." Molecular Microbiology **5**(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. The skilled artisan further recognizes that immunological responses may depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted. Thus, both biological function and immunological recognition are unpredictable properties which must be experimentally determined. Further it is noted, that for particularly small peptides, conjugation appears to be required for promoting an effective immune response.

21. On the level of predictability in the art, Greenfield *et al.* (1999) "Regulation of Osteoclast Activity." Life Sciences **65**(11): 1087-1102 teaches that the balance between bone formation and resorption is the result of a complex interaction of indirect and direct inhibitors and activators. As little as a 20% increase in bone resorption can lead to the debilitating effects of osteoporosis (pp. 1087; Table 1). As discussed above, perturbation of this balance can have undesired and unpredictable effects. Absent concrete guidance on the structure and position of B-cell or T-cell epitope placement in OPGL and the ensuing immune response, the skilled artisan is confronted with an unpredictable endeavor to fulfill the claims to the full extent of the possible OPGL-B-cell/T-cell epitope combinations.

22. On the state of the prior art, Tsukii *et al.* (19 May 1998) "Osteoclast Differentiation Factor Mediates an Essential Signal for Bone Resorption Induced by 1 α ,25-Dihydroxyvitamin D₃, Prostaglandin E₂, or Parathyroid Hormone in the Microenvironment of Bone." Biochemical and Biophysical Research Communications 246(2): 337-341 teaches that administration of rabbit anti-ODF polyclonal antibodies in a fetal long bone culture experiment blocks ODF (also known as OPGL herein) activity (Figure 2). While this lends credence to the invention in concept, it does not offer guidance on how to replicate similar results *in vivo* via active immunization wherein the animal's immune system down regulates endogenous OPGL. Further, Goldsby *et al.* (2002) Kuby Immunology Chapter 18 "Vaccines" (pp. 449-465) teaches that active immunization is not predictable as peptides are not generally immunogenic.

23. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *suggestion* and *indirect evidence* to extent the claimed method beyond what is disclosed as exemplified in the references herein.

24. Claims 1, 3, 5, 8-12, 17-24, 57, and 58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

25. The claims recites B-cell epitopes containing subsequences of OPGL with various changes but does require that the entity to possess any particular conserved structure, or other distinguishing feature. Thus, the claims are drawn to a genus of agents that is defined by a myriad of possible B-cell/OPGL combinations.

26. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a recitation of full-length OPGL (SEQ ID NO: 2) and OPGL fragments consisting of residues 128-316, 137-316, and 158-316 from the sequence of SEQ ID NO: 2. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

27. To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that “the inventor invented the claimed invention”); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) (“the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed”). Thus, an applicant complies with the written-description requirement “by describing the invention, with all its claimed limitations, not that which makes it obvious.”

and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572.

28. See *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003) and *University of Rochester v. G.D. Searle & Co. et al.* CAFC [(03-1304) 13 February 2004]. In *University of Rochester v. G.D. Searle & Co.* a patent directed to method for inhibiting prostaglandin synthesis in human host using an unspecified compound, in order to relieve pain without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since the patent described the compound's desired function of reducing activity of the enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since invention consists of performing "assays" to screen compounds in order to discover those with desired effect. The patent did not name even one compound that assays would identify as suitable for practice of invention, or provide information such that one skilled in art could identify suitable compound. And since specification did not indicate that compounds are available in public depository, the claimed treatment method cannot be practiced without compound. Thus the inventors cannot be said to have "possessed" claimed invention without knowing of a compound or method certain to produce compound. Thus said patent constituted an invitation to experiment to first identify, then characterize, and then use a therapeutic a class of compound defined only by their desired properties.

29. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Summary

30. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

CJN
April 23, 2004